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Préparation à base de microparticules et production de celle-ci

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(73) Proprietor: TAKEDA CHEMICAL INDUSTRIES, LTD.
Chuo-ku, Osaka 541 (JP)

(72) Inventors:
- Akagi, Yasaburo
Takatsuki, Osaka 569 (JP)
- Takechi, Nobuyuki
Osaka 533 (JP)
- Nonomura, Muneo
Suita, Osaka 565 (JP)

(74) Representative: Hall, Marina et al
Elkington and Fife
Prospect House,
8 Pembroke Road
Sevenoaks, Kent TN13 1XR (GB)

(56) References cited:
EP-A- 0 452 862
EP-A- 0 570 606
WO-A-85/03000
GB-A- 1 465 781
GB-A- 2 145 422
GB-A- 2 234 896
JP-A- 2 164 439
JP-A- 5 112 815
JP-A- 85 110 831
US-A- 4 486 435
US-A- 4 652 441
US-A- 4 711 782
US-A- 4 912 146
US-A- 4 954 298
US-A- 5 061 492

- Handbook of Chemistry and Physics, 49th ed., pp. B186, B214 (1968)
- The Merck Index, 11th ed., p. 251 (1989)
- Encyclopedia of Chemical Technology, vol. 2, p. 461 (1948)
- Ogawa, J. Biomater. Sci. Polymer Edn. Vol. 8 N° 5, pp. 391-409 (1997)

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Description

FIELD OF THE INVENTION

[0001] The present invention relates to a microcapsule preparation comprising microcapsules of a biodegradable poly fatty acid ester which contain a drug and are wholly coated with an inorganic salt, an organic acid or a salt of organic acid for preventing aggregation of the microcapsules (hereinafter sometimes referred to as a microcapsule preparation) and the production thereof by spray drying.

BACKGROUND OF THE INVENTION

[0002] The traditional microcapsulation method which comprises formation of a three-phase emulsion containing a drug, followed by microcapsulation thereof by in-water drying process to obtain microcapsules is mentioned in JP-A-60-100516 (U.S. Patent No. 4,652,441). Although this technique improves the above disadvantage of adhesion, some points to be improved still remain. Namely, it is difficult to obtain microcapsules having a high drug content because, in the case of a water-soluble drug, the drug leaks out to the outer aqueous phase and the entrapping ratio thereof drops. Further, in general, the microcapsules thus obtained have a large initial release rate of a drug. Furthermore, the microcapsules tend to be readily influenced by scaling up of the production and large scale treatment is difficult.

[0003] Furthermore, EP-A-0 315 875 discloses microparticles prepared by spray drying which comprise a polymer and a drug. This reference further refers to the fact that as a release enhancer, water-soluble inorganic salts may be present. However, no disclosure is made of microparticles which are at least partially coated by such an inorganic salt.

[0004] On the other hand, there are reports relating to microparticles produced by spray drying with one nozzle. However, in any of these reports, the initial release of a drug, the so called initial burst of a drug from the microparticles is large and the desired prolonged release over a long period of time is not achieved. Further, the time which is needed to disperse the microparticles completly and uniformly of the microparticles to an aqueous dispersing agent is to be improved. Furthermore, there is a problem that a large amount of microparticles often aggregate to each other and adhere to a spray dryer.

SUMMARY OF THE INVENTION

[0005] Under these circumstances, the present inventors have made intensive studies to develop water-soluble or fat-soluble microcapsule preparations having a lower aggregation or adhesion property and a good dispersibility. As a result, it has been found that microcapsule preparation having a high entrapping ratio of a drug, a small initial burst of a drug and excellent properties can be obtained efficiently and continuously in a large amount in a short period of time by atomizing and spraying (1) a solution containing a drug and a polymer, (2) a dispersion solution in which a part or whole of a drug or polymer is in a solid state, (3) an O/W, W/O, W/O/W or O/W/O type emulsion comprises a solution containing a drug and/or a polymer or (4) an O/W, W/O, W/O/W or O/W/O type emulsion comprises a dispersion solution in which a part or whole of a drug or a polymer is in a state of dispersion from one nozzle of spray dryer (two-fluid nozzle, multi-fluid nozzle, pressure nozzle or rotary disc for two or more-liquid spraying) and by spraying a solution of a non-adhesive water-soluble inorganic salt, organic acid or salt of organic acid, as an agent for preventing aggregation of the microcapsule preparation from the other nozzle. Said solution of the inorganic salt, organic acid or salt of the organic acid may include a suspension thereof.

[0006] Further, it has been found that microcapsules having a good dispersibility can be obtained by (1) spraying a solution containing a non-ionic surfactant in addition to the inorganic salt, organic acid or salt of the organic acid or (2) further spraying a solution containing a non-ionic surfactant and the solution containing the inorganic salt, organic acid or salt of the organic acid simultaneously.

[0007] After further studies based on this findings, the present invention has been completed.

[0008] The present invention provides a microcapsule preparation comprising microcapsules of a biodegradable poly fatty acid ester which contain a drug and are wholly coated with a water-soluble inorganic salt, water-soluble organic acid or a water-soluble salt of an organic acid but in which the water-soluble organic acid is not carboxymethylcellulose or an amino acid and the water-soluble salt of an organic acid is not a salt of carboxymethylcellulose.

[0009] Further, the present invention provides a process for the production of a microcapsule preparation comprising spraying a solution of a biodegradable poly fatty acid ester containing a drug and a solution of a water-soluble inorganic salt, water-soluble organic acid or water-soluble salt of an organic acid separately from different nozzles wherein the water-soluble organic acid is not carboxymethylcellulose or an amino acid and the water-soluble salt of an organic acid is not a salt of carboxymethylcellulose, and contacting them with each other in a spray dryer to produce microcapsules of the biodegradable poly fatty acid ester which contain the drug and are wholly coated with the inorganic salt, the organic acid or the salt of the organic acid.

[0010] In the above production of microcapsule preparations of this invention, a microcapsule preparation having a good dipersibility can be obtained by (1) spraying a solution containing a non-ionic surfactant in addition to the inorganic salt, organic acid or salt of the organic acid or (2) further spraying a solution containing a non-ionic surfactant and the solution containing the inorganic salt, organic acid or salt of the organic acid simultaneously.

[0011] According to the present invention, it is possible to produce a microcapsule preparation having a desired and strong structure with minimizing loss of a drug by spray-drying the solution, emulsion or suspension containing a drug and a biodegradable poly fatty acid ester by using a spray dryer to volatilize water as well as an organic solvent in a moment. Further, it is possible to reduce the initial burst of a drug to a smaller amount than that of the in-water drying process. Furthermore, it is possible to obtain powder particles having excellent fluidity in a short period of time without employing any freeze-drying step by spraying the solution of the inorganic salt, the organic acid or the salt of the organic acid from another nozzle at the same time to coat at least partially or wholly the surface of the microcapsules with the inorganic salt, organic acid or salt of the organic acid, thereby preventing aggregation of the microcapsules with each other and adhesion of the microcapsules to a spray dryer. In addition to the foregoing, a microcapsule preparation having a good dipersibility can be obtained by (1) spraying a solution containing a non-ionic surfactant in addition to the inorganic salt, organic acid or salt of the organic acid or (2) further spraying a solution containing a non-ionic surfactant and the solution containing the inorganic salt, organic acid or salt of the organic acid simultaneously.

DETAILED DESCRIPTION OF THE INVENTION

[0012] The drug to be used in the present invention is not specifically limited. Examples thereof include peptides having biological activities, other antibiotics, antitumor agents, antipyretics, analgesics, anti-inflammatory agents, antitussive expectorants, sedatives, muscle relaxants, antiepileptic agents, antiulcer agents, antidepressants, antiallergic agents, cardiotonics, antiarrhythmic agents, vasodilators, hypotensive diuretics, antidiabetic agents, anticoagulants, hemostatics, antituberculous agents, hormone preparation, narcotic antagonists, bone resorption inhibitors, angiogenesis inhibiting substances and the like.

[0013] Among these drugs, preferred examples include peptides having biological activities, bone resorption inhibitors and angiogenesis inhibiting substances.

[0014] The peptides having biological activities to be used in the present invention are those having two or more amino acids, preferably having molecular weight of about 200 to 80,000.

[0015] Examples of the peptide include luteinizing hormone-releasing hormone (LH-RH), its derivatives having similar acitivity, i.e., a peptide of the formula (I):

$$(Pyr)Glu\text{-}R^1\text{-}Trp\text{-}Ser\text{-}R^2\text{-}R^3\text{-}R^4\text{-}Arg\text{-}Pro\text{-}R^5 \qquad (I)$$

wherein R^1 is His, Tyr, Trp, or p-NH_2-Phe; R^2 is Tyr or Phe; R^3 is Gly or D-amino acid residues; R^4 is Leu, Ile or Nle; and R^5 is Gly-NH-R^6 (wherein R^6 is H or lower alkyl optionally substituted with hydroxyl) or NH-R^6 (wherein R^6 is as defined above), or a salt thereof [see, U.S. Patent Nos. 3,853,837, 4,008,209 and 3,972,859; G.B. Patent No. 1,423,083: and Proc. Nat. Acad: Sci. U.S.A., vol. 78, pp. 6509-6512 (1981)].

[0016] As the D-amino acid residue represented by R^3 in the above formula (I), there are, for example, α-D-amino acids having up to 9 carbon atoms [e.g., D-(Leu, Ile, Nle, Val, NVal, Abu, Phe, Phg, Ser, Tyr, Met, Ala, Trp, α-Aibu, etc.), etc] and the like. These residues may have suitable propective groups (e.g., t-butyl, t-butoxy, t-butoxycarbonyl, etc). The acid addition salts and metal complexes of the peptide of the formula (I) [hereinafter referred to as the peptide (I)] can be used in the same manner as the peptide (I).

[0017] The abbreviation of amino acids, peptides, protective groups, etc. in the peptide (I) are those establised by IUPAC-IUB Commission on Biochemical Nomenclature or those commonly used in the art. When optical isomers of amino acids are present, the amino acids are represented as L-isomers unless otherwise indicated.

[0018] In the present specification, the acetic acid salt of the peptide (I) [wherein R^1 is His, R^2 is Tyr, R^3 is D-Leu, R^4 is Leu and R^5 is $NHCH_2$-CH_3] is referred to as "TAP-144".

[0019] Example of the peptide (I) include LH-RH antagonists (see U.S. Patent Nos. 4,086,219, 4,124,577, 4,253,997 and 4,317,815).

[0020] Further examples of the peptides having biological acitvities include oligopeptides such as insulin, somatostatin, somatostatin derivatives (see U.S. Patent Nos. 4,087,390, 4,093,574, 4,100,117 and 4,253,998), growth hormone, prolactin, adrenocorticotropic hormone (ACTH), melanocyte-stimulating hormone (MSH), thyrotropin-releasing hormone (TRH), their salts and derivatives (see JP-A 50-121273 and JP-A 52-116465), thyroid-stimulating hormone (TSH), luteinizing hormone (LH), follicle-stimulation hormone (FSH), vasopressin, vasopressin derivatives (desmopressin [see Folia Endocrinologica Japonica, vol. 54, No. 5, pp. 676-691 (1978)]), oxytocin, calcitonin, parothyroid

hormone, glucagon, gastrin, secretin, pancreozymin, cholecystokinin, angiotensin, human placental lactogen, human chorionic gonadotropin (HCG), enkephalin, enkephalin derivatives (see U.S. Patent No. 4,277,394 and EP-A 31,567); and polypeptides such as endorphin, kyotorphin, interferon (α-type, β-type, γ-type), interleukin (I to XI), tuftsin, thymopoietin, thymosin, thymostimulin, thymic hormone factor (THF), serum thymic factor (FTS) and derivatives thereof (see U.S. Patnet No. 4,299,438) and other thymic factors [see Medicine in Progerss, vol. 125, No. 10, pp. 835-843 (1983)], tumor necrosis factor (TNF), colony stimulating factor (CSF), motilin, deinorphin, bombesin, neurotensin, caerulein, bradykinin, urokinase, asparaginase, kallikrein, substance P, nerve growth factor, blood coagulation factor VIII and IX, lysozyme chloride, polymyxin B, colistin, gramicidin, bacitracin, protein synthesis-stimulating peptide (see G. B. Patent No. 8,232,082), gastric inhibitory polypeptide (GIP), vasoactive intestinal polypeptide (VIP), platelet-derived growth factor (PDGH), growth hormone-releasing factor (GRF, somatoclinine), bone morphogenic protein (BMP), epidermal growth hormone (EGF) and the like.

[0021] Example of the above antitumor agent include bleomycin hydrochloride, methotrexate, actinomycin D, mitomycin C, vinblastine sulfate, vincristine sulfate, daunorubicin hydrochloride, adriamycin, neocarcinostatin, cytosine arabinoside, fluorouracil, tetrahydrofuryl-5-fluorouracil, picibanil, lentinan, levamisole, bestatin, azimexon, glycyrrhizin, poly A:U, poly ICLC and the like.

[0022] Example of the above atibiotics include gentamicin, dibekacin, kanendomycin, lividomycin, tobromycin, amikacin, fradiomycin, sisomysin, tetracycline, oxytetracycline, roliteracydine, doxycycline, ampicillin, piperacillin, ticarcillin, cefalotin, cefaloridine, cefotiam, cefsulodin, cefmenoxime, cefmetazole, cefazolin, cefataxim, cefoperazone, ceftizoxime, moxolactame, thienamycin, sulfazecine, azusleonam, salts thereof, and the like.

[0023] Examples of the above antipyretic, analgesic and anti-inflammatory agents include salicylic acid, sulpyrine, flufenamic acid, diclofenac, indometacin, morphine, pethidine, levorphanol tartrate, oxymorphone and the like.

[0024] Examples of the antitussive expectorant include ephedrine, methylephedrine, noscapine, codeine, dihydrocodeine, allociamide, chlorphezianol, picoperidamine, cloperastine, protokylol, isoproterenol, salbutamol, terebutaline, salts thereof and the like.

[0025] Examples of the sedative include chlorpromazine, prochloperazine, trifluoperazine, atropine, scopolamine, salts thereof and the like.

[0026] Examples of the muscle relaxant include pridinol, tubocurarine, pancuronium and the like.

[0027] Examples of the antiepileptic agent include phenytoin, ethosuximide, acetazolamide, chlordiazepoxide and the like.

[0028] Examples of the antiulcer agent include metoclopramide, histidine and the like.

[0029] Examples of the antidepressant include imipramine, clomipramine, onxiptiline, phenelzine and the like.

[0030] Examples of the antiallergic agent include diphenhydramine hydrochloride, chlorpheniramine malate, tripelennamine hydrochloride, methdilazine hydrochloride, demizole hydrochloride, diphenylpyraline hydrochloride, methoxyphenemine hydrochloride and the like.

[0031] Examples of the cardiotonic include transpieoxocamphor, terephylol, aminophylline, etilefrin and the like.

[0032] Examples of the antiarrythmic agent include propranolol, alprenolol, bufetolol, oxyprenolol and the like.

[0033] Examples of the vasodilator include oxyfedrine, diltiazem, tolazoline, hexobendine, bamethan and the like.

[0034] Examples of the hypotensive diuretic include hexamethonium bromide, pentolinium, mecamylamine, ecarazine, clonidine and the like.

[0035] Examples of the antidiabetic agent include glymidine, glipizide, phenformin, buformin, metformin and the like.

[0036] Examples of the anticoagulant include heparin, citric acid and the like.

[0037] Examples of the hemostatic include thromboplastin, thrombin, menadione, acetomenaphthone, ε-aminocaproic acid, tranexamic acid, carbazochrome sulfonate, adrenochrome monoaminoguanidine and the like.

[0038] Examples of the antituberculous agent include isoniazid, ethambutol, para-aminosalicylic add and the like.

[0039] Examples of the hormone preparation include prednisolone, dexamethasone, betametasone, hexestrol, methymazole and the like.

[0040] Examples of the narcotic antagonist include levallorphan, nalorphine, naloxone, salts thereof and the like.

[0041] Examples of the bone resorption inhibitors include (sulfur-containing alkyl) aminomethylenebisphosphonic acid and the like.

[0042] Examples of the angiogenesis-inhibiting substance include angiostatic steroid [Science, 221, 719 (1983)], fumagillin (e.g., EP-A-325199, etc.), fumagillol derivatives (e.g., EP-A-357061, EP-A-359036, EP-A-386667, EP-A-415294, etc.) and the like.

[0043] Among these drugs, this invention can be preferably applicable to a water-soluble drug, since a water-soluble drug is apt to be released excessively at the initial stage of administration.

[0044] A solubility in water of the water-soluble drug of the present invention depends on an n-octanol/water partition coefficient.

[0045] In the present invention, an n-octanol/water partition coefficient of the water-soluble drug is preferably not more than 1, more preferably not more than 0.1.

[0046] The n-octanol/water partition coefficient can be determined by the method described in Robert E. Notari, "Biopharmaceutics and Pharmacokinetics", Marcel Dekker Inc., 1975, New York, U.S.A. Thus, equal amounts of n-octanol and a buffer solution (pH 5.5) are placed in a test tube to give a 1:1 mixture. The buffer solution is exemplified by Sörensen buffer [Engebnisse der Physiology 12, 393 (1912)], Clark-Lubs buffer [Journal of Bacteriology 2, (1), 109, 191 (1971)], Macllvaine buffer [Journal of Biological Chemistry 49, 183 (1921)], Michelis buffer [Die Wasser Stoffionenkonzentration, p. 186 (1914)], Kolthoff buffer [Biochemische Zeitschrift 179, 410 (1926)] and so on. An adequate amount of the drug to be tested is added to the mixture, and the test tube is stoppered, immersed in a constant-temperature bath (25°C) and shaken vigorously. When it appears that the drug has been dissolved in between both the liquid layers and an equilibrium has been reached, the mixture is allowed to stand or is centrifuged, and aliquots of the upper and lower liquid layer are pipeted separately and analyzed for the concentration of the drug in each layer. The ratio of the concentration of the drug in the n-octanol layer to the concentration of the drug in the aqueous layer is the n-octanol/water partition coefficient

[0047] These drugs themselves and their pharmaceutically acceptable salts can be used in the present invention.

[0048] Examples of the pharmaceutically acceptable salts of the drugs include a salt with an inorganic acid (e.g., hydrochloric acid, sulfuric acid, nitric acid, etc.) a salt with an organic acid (e.g., carbonic acid, citric acid, etc.) , when the drugs have a basic residue such as an amino group and so on. Examples of the pharmaceutically acceptable salts of the drugs include a salt with an inorganic base (e.g., alkaline metal such as sodium, potassium and so on), organic basic compound (e.g., triethylamine, pyridine, etc.), basic amino acid (e.g., arginine, histidine, etc.) and so on, when the drugs have an acidic residue such as a carboxyl group and so on.

[0049] The amount of the above drugs to be used depends on a particular kind of drug, desired pharmacological activity, duration time and the like. The concentration of the drugs in the solution to be sprayed, for example, is about 0.001% to about 70% (W/W), preferably about 0.01% to about 50% (W/W).

[0050] The biodegradable poly fatty acid ester in the present invention is slightly water-soluble or water-insoluble, and has biocompatibility. "Slightly water-soluble" means that solubility of the polymer in water does not exceed about 3% (W/W).

[0051] The amount of the biodegradable poly fatty acid ester to be used depends on a particular strength of the pharmacological activity of the drug, release rate and period of the drug and the like. For example, the biodegradable poly fatty acid ester is used in an amount of 0.5 to 1,000 times the weight of the drug. Preferably, the biodegradable poly fatty acid ester in an amount of about 1 to 100 times the weight of the drug is used.

[0052] The weight-average molecular weight of the biodegradable poly fatty acid ester to be used may be selected from the range of about 3,000 to 30,000, preferably about 5,000 to 25,000, more preferably about 5,000 to 20,000.

[0053] The dispersity of the biodegradable poly fatty acid ester to be used may be selected from the range of about 1.2 to 4.0, preferably about 1.5 to 3.5, more preferably about 1.5 to 2.5.

[0054] The weight-average molecular weight and dispersity of the polymer in the present specification are determined by gel permeation chromatography (GPC) in terms of polystyrene as a standard. In the determination, GPC column KF804X2 (Shyowadenko, Japan) is used and chloroform is used as a mobile phase.

[0055] Examples of biodegradable poly fatty acid esters include [e.g., homopolymer of fatty acid (e.g., polylactic acid, polyglycolic acid, polycitric acid, polymalic acid, etc.) or copolymer of two or more fatty acids (e.g., copolymer of lactic acid/glycolic acid, copolymer of 2-hydroxybutyric acid/glycolic acid, etc.), a mixture of the homopolymer and/or copolymer (e.g., mixture of poly lactic acid and copolymer of 2-hydroxybytyric acid/glycolic acid, etc.), example of the fatty acid include, α-hydroxycarboxylic acid (e.g., glycolic acid, lactic acid, 2-hydroxybutyric acid, 2-hydroxyvaleric acid, 2-hydroxy-3-methylbutyric acid, 2-hydroxycaproic acid, 2-hydroxyisocaproic acid, 2-hydroxycaprylic acid, etc.), cyclic dimers of α-hydroxycarboxylic acids (e.g., glycolide, lactide, etc.), hydroxydicarboxylic acid (e.g., malic acid, etc.), hydroxytricarboxylic acid (e.g., citric acid, etc.) and so on]. These polymers may be used alone or in combination thereof. They may be used in the form of a copolymer or mere mixture of these two or more polymers. They may be in the form of salts thereof.

[0056] Among poly fatty acid esters, in particular, homopolymers of α-hydroxycarboxylic acids, cyclic dimers of α-hydroxycarboxylic acids; copolymers of two or more α-hydroxycarboxylic acids, cyclic dimers of α-hydroxycarboxylic acids; and a mixture of the homopolymers and/or the copolymers are preferred. More preferred examples include homopolymers of α-hydroxycarboxylic acids; copolymers of two or more α-hydroxycarboxylic acids; and a mixture of the homopolymers and/or the copolymers. Most preferred examples include polylactic acid, copolymer of lactic acid/glycolic acid, copolymer of 2-hydroxybutyric acid/glycolic acid and a mixture thereof.

[0057] When these α-hydroxycarboxylic acids, cyclic dimers of α-hydroxycarboxylic acids, hydroxydicarboxylic acids, hydroxytricarboxylic acids may be D-, L- or D,L-configurated, the D-, L- and D,L-compounds can be used equally.

[0058] When a copolymer of lactic acid/glycolic acid is used as one example of the above polymer, its composition (monomer) ratio is preferably about 100/0 to 50/50 (mole/mole), when a copolymer of 2-hydroxybutyric acid/glycolic acid is used as one example of the above polymer, its composition (monomer) ratio is preferably about 100/0 to 25/75 (mole/mole).

[0059] The weight-average molecular weight of the copolymer of lactic acid/glycolic acid is preferably about 3,000 to 30,000, more preferably about 5,00 to 20,000.

[0060] When a mixture of a polylactic acid (A) and a copolymer of 2-hydroxybutyric acid/glycolic acid (B) is used as one example of the above polymers, the mixture can be used in a blend ratio of about 10/90 to 90/10 (by weight), preferably about 25/75 to 75/25 (W/W).

[0061] The weight-average molecular weight of the polylactic acid (A) is preferably about 3,000 to 30,000, more preferably about 5,000 to 20,000.

[0062] The preferred proportion of glycolic acid in the copolymer (B) is in the range of about 40 to 70 mole%.

[0063] The weight-average molecular weight of the copolymer (B) is preferably about 5,000 to 25,000, more preferably about 5,000 to 20,000.

[0064] As the water-soluble inorganic salt, the organic acid or the salt of organic acid, which is used as an aggregation-preventing agent in the present invention, there can be used water-soluble materials which are applicable to humans, solid at room temperature (about 15 to 25°C) and non-adhesive in their dried state.

[0065] Examples of the water-soluble inorganic salts include halogenated alkali metal (e.g., sodium chloride, potassium chloride, sodium bromide, potassium bromide, etc.), halogenated alkali-earth metal (e.g., calcium chloride, magnesium chloride, etc.), halogenated ammonium (e.g., ammonium chloride, ammonium bromide, etc.), alkali metal carbonate or alkali metal hydrogencarbonate (e.g., sodium carbonate, potassium carbonate, sodium hydrogen carbonate, potassium hydrogen carbonate, etc.), alkali-earth metal carbonate (e.g., calcium carbonate, magnesium carbonate, etc.) ammonium carbonate, ammonium hydrogen carbonate, alkali metal phosphate (e.g., trisodium phosphate, tripotassium phosphate, disodium hydrogen phosphate, dipotassium hydrogen phosphate, sodium dihydrogen phosphate, potassium dihydrogen phosphate, etc.), diammonium hydrogen phosphate, ammonium dihydrogen phosphate, alkali-earth metal oxide (e.g., magnesium oxide, calcium oxide, etc.), alkali-earth metal hydroxide (e.g., magnesium hydroxide, calcium hydroxide, etc.) and the like.

[0066] Examples of the water-soluble organic acid include citric acid, tartaric acid, malic acid, succinic acid, benzoic acid, chondroitin sulfuric acid, dextran sulfuric acid, alginic acid, pectic acid and the like.

[0067] Examples of the water-soluble salt of organic acid include alkali metal (e.g., sodium, potassium, etc.) or alkali-earth metal (e.g., calcium magnesium, etc.) salts of organic acid (e.g., acetic acid, citric acid, tartaric acid, malic acid, succinic acid, benzoic acid chondroitin sulfuric acid, dextran sulfuric acid, alginic acid, pectic acid, etc.) and the like.

[0068] Among these, a water-soluble inorganic salt can be advantageously used.

[0069] These can be used alone or in combination thereof in an appropriate ratio.

[0070] The weight ratio of the water-soluble inorganic salt, organic acid and salt of organic acid to the polymer can be in the range wherein the desired aggregation-preventing effect is obtained. The weight ratio, for example, is about 0.001 to 100 times, preferably about 0.01 to 50 times, more preferably about 0.1 to 10 times the weight of the polymer.

[0071] In the present invention, if desired, a microcapsule preparation, wherein surfactant is dispersed or coated thereon to give a good dipersibility thereto, can be obtained by (1) spraying a solution containing a surfactant in addition to an inorganic salt, an organic acid or a salt of an organic acid or (2) further spraying a solution containing a surfactant and a solution containing an inorganic salt, an organic acid or a salt of an organic acid simultaneously.

[0072] Examples of the surfactant include a non-ionic surfactant [e.g., alkyleneglycol (e.g., propylene glycol, etc.), polysorbate (e.g., polysorbate 400, polysorbate 60, polysorbate 80, etc.), Macrogol (e.g., Macrogol 300, Macrogol 400, Macrogol 600, Macrogol 1500, Macrogol 4000, Macrogol 6000, etc.), polyoxyethylene hydrogenated castor oil (e.g., polyoxyethylene hydrogenated castor oil 10, polyoxyethylene hydrogenated castor oil 50, polyoxyethylene hydrogenated castor oil 60, etc.), and so on] and the like.

[0073] These can be used alone or in combination thereof in an appropriate ratio.

[0074] The weight ratio of the surfactant to the polymer can be in the range wherein the improved dispersibility is obtained, The weight ratio, for example, is about 0.0000001 to 10 times, preferably about 0.000005 to 5 times, more preferably about 0.00001 to 0.01 times the weight of the polymer.

[0075] As is mentioned above, microcapsule preparations of the present invention can be produced by atomizing and spraying (1) a solution containing a drug and a polymer, (2) a dispersion solution in which a part or whole of a drug or polymer is in a state of dispersion, (3) an O/W, W/O, W/O/W or O/W/O type emulsion comprising a solution containing a drug and/or a polymer or (4) an O/W, W/O, W/O/W or O/W/O type emulsion comprising a dispersion solution in which a part or whole of a drug or a polymer is in a state of dispersion from one nozzle of a spray dryer and by spraying a solution of a non-adhesive water-soluble inorganic salt, organic acid or salt of organic acid, as a preparation, including microcapsules, from the other nozzle. Further, if desired, it may (1) spray a solution containing a non-ionic surfactant in addition to a water-soluble inorganic salt, a water-soluble organic acid or a water-soluble salt of an organic acid or (2) spray a solution containing a non-ionic surfactant and a solution containing the organic salt, organic acid or salt of the inorganic acid simultaneously.

[0076] An aqueous solution of the inorganic salt, organic acid or salt of the organic acid can be preferably used.

[0077] In the production of the microcapsule preparation of the present invention, for example, when a drug is water-

soluble, the drug is dissolved in water to prepare an aqueous solution for an internal aqueous phase. As a pH adjustor to maintain the stability or solubility of the water-soluble drug, for example, an inorganic acid (e.g., carbonic acid, phosphoric acid, etc.), an organic acid (e.g., acetic acid, oxalic acid, citric acid, tartaric acid, succinic acid, etc.), alkali metal (e.g., sodium, potassium, etc.) salt of the inorganic acid or organic acid, hydrochloric acid, alkali metal hydroxide (e.g., sodium hydroxide, etc.) and the like can be added to the aqueous solution. Further, as a stabilizer of the water-soluble drug, there can be added, for example, albumin, gelatin, citric acid, sodium ethylenediamine tetraacetate, dextrin, sodium hydrogensulfite or the like, Furthermore, as a preservative, there can be added, for example, parahydroxybenzoic acid esters (e.g., methylparaben, propylparaben, etc.), benzyl alcohol, chlorobutanol, thimerosal and the like.

[0078] The solution for the internal aqueous phase thus obtained is added to a solution (oil phase) containing the polymer, followed by emulsification to prepare a W/O type emulsion.

[0079] As the solution containing the above polymer, a solution of the polymer dissolved in an organic solvent is used.

[0080] As the organic solvent, there can be used any solvent whose boiling point is not more than about 120°C and which is slightly miscible with water and can dissolve the polymer. Examples the organic solvent include halogenated alkanes (e.g., dichloromethane, carbon tetrachloride, etc.), fatty acid ester (e.g., ethyl acetate, butyl acetate, etc.), ethers (e.g., ethyl ether, isopropyl ether, etc.), hydrocarbons (e.g., cyclohexane, n-hexane, pentane, etc.), aromatic hydrocarbons (e.g., benzene, toluene, etc.) and the like. These solvent can be used alone or in combination thereof in an appropriate ratio.

[0081] The emulsification can be carried out by dispersion techniques. For example, intermittent shaking, mixing by means of a mixer such as a propeller agitator, turbine agitator or the like, colloid mill operation, mechanical homogenization ultrasonication and the like.

[0082] In the W/O type emulsion, the ratio of the internal aqueous phase to the oil phase depends on a kind of solvent or a particular kind of drug. The preferable ratio of the internal aqueous phase to the oil phase can be in the range of about 5 to 95% (W/W), more preferably about 10 to 30% (W/W).

[0083] Alternatively, the drug (which may be water-soluble or fat-soluble) and polymer are dissolved in an organic solvent or a mixture of a solvent miscible with water and water. When the drug is insoluble the mixture is subjected to suspending operation to prepare a S/O type suspension containing finely pulverized drug particles. As the organic solvent in this case, in addition to the aforementioned organic solvents, there can be used solvents readily miscible with water such as acetone acetonitrile, tetrahydrofuran, dioxane, pyridine, alcohols (e.g., methanol, ethanol, etc.) or the like. These solvent can be used alone or in combination thereof in an appropriate ratio. There can be used a mixture having a suitable mixing ratio of water and the above organic solvent The ratio depends on a kind of solvent or a particular kind of drug. The preferable ratio of the water to the organic solvent can be in the range of about 1 to 99% (V/V), more preferably about 5 to 90% (V/V), most preferably about 10 to 30% (V/V).

[0084] Then, the emulsion, suspension, solution or suspended emulsion thus obtained is sprayed into a drying chamber of a spray dryer through a nozzle, and the organic solvent and water in the atomized droplets are removed in an extremely short period of time to prepare a powdered microcapsules preparation. As the nozzle, a two-liquid type nozzle multi-fluid type nozzle, pressure type nozzle, rotary type nozzle or the like can be used. At the same time, in order to prevent aggregation of the microparticles, an aqueous solution of a water-soluble inorganic acid, organic acid or salt of an org anic acid is sprayed from another nozzle. Namely, two nozzles are provided, and the emulsion, suspension, solution or suspended emulsion containing drug and polymer is sprayed from one nozzle, while the aqueous solution of the inorganic salt, organic acid or salt of the organic acid is sprayed from the other nozzle to disperse it on the surface of the microcapsules. When a two-liquid type nozzle or pressure type nozzle is used as the nozzle, the two nozzles may be provided in the center of a spray dryer. Preferably, a nozzle having the structure suitable for two-liquid spraying is used so that the solution containing the drug and polymer and the aqueous solution of the inorganic salt, organic acid or salt of the organic acid can be sprayed separately without mixing them in the nozzle.

[0085] In the above production method, a solution containing a non-ionic surfactant in addition to the inorganic salt, organic acid or salt of the organic acid can be sprayed. Further, a solution containing a non-ionic surfactant and the solution containing the inorganic salt, organic acid or salt of the organic acid can be sprayed from the other separate nozzle simultaneously.

[0086] The conditions for spraying can be suitably determined according to a kind of microparticle or a kind of spray dryer.

[0087] The microcapsule preparations thus obtained are subjected to removal of water and the solvent in the microparticle preparations more completely under reduced pressure, if necessary, with warming under reduced pressure.

[0088] The particle size of the microparticle preparations depends on the desired degree of prolonged release and the kind of preparation. When the particles are used in a form of an injectable suspension, for example, the particle size can be in the range which satisfies their dispersibility and needle pass requirements. For example, the average diameter is preferably the range of about 0.5 to 400 μm, more preferably about 2 to 200 μm.

[0089] The microcapsule preparations of the present invention have many advantages. For example, because the

non-adhesive water-soluble inorganic salt, organic acid, salt of the organic acid is dispersed on the surface of the microparticle preparations, aggregation of the microcapsules preparations with each other is little in the course of production, and even globular microcapsules preparation can be obtained. When a non-ionic surfactant is used, the microcapsules preparations show an excellent dispersibility in a dispersing agent.

[0090] Furthermore, according to the process of the present invention, the take-up ratio of the drug into the microcapsules preparation can be increased up to the about 100% without any loss of the active component which is apt to provide in the in-water drying process. Further, the amount of the organic solvent to be used is smaller than that of the in-oil drying process. Furthermore, although it takes an extremely long period of time to remove the solvent in the in-water drying process, this time can be extremely reduced. Thus, the process of the present invention is extremely useful for the industrial production.

[0091] The microcapsule preparation of the present invention has low toxicity and can be used safely.

[0092] The microcapsule preparation can be used for treatment or prevention of the various diseases according to the kind of the drug being contained therein. For example, when the drug is a LH-RH derivative, the microcapsules preparation can be use for treatment of prostate cancer or endometriosis; when the drug is TRH, the microcapsules preparation can be used for treatment of senile dementia or spinal cerebellum degeneration; when the drug is (sulfur-containing alkyl)aminomethytenebisphosphonic acid, the microcapsule preparation can be used for treatment or prevention of osteoporosis.

[0093] The microcapsule preparation of the present invention can be administered as it is into the living bodies as powder formulation, or by molding them in the form of various preparations. Further, the microcapsule preparation can be used as raw materials in the production of various preparations.

[0094] As the above mentioned preparation, for example, parenteral preparation [e.g., injectable preparation, topical preparation (e.g., nasal preparation, dermatological preparation, etc.), suppositories (e.g., rectal, vaginal), etc.], oral preparation (e.g., powders, granules, capsules, tablets, etc.) and so on can be mentioned. The amount of drug to be included in the preparations depends on the kind of the drug, dosage form, object of treatment, and so on. However, the amount of drug per dosage form may usually be selected from the range of about 0.001 mg to 5 g, preferably about 0.01 mg to 2 g. For example, in case the drug is TRH, TRH derivative or a salt thereof, the amount of the drug per dosage form may usually be selected from the range of about 0.1 mg to 1 g, preferably about 1 mg to 500 mg, more preferably about 3 mg to 60 mg.

[0095] These preparations can be manufactured by using per se known methods in the field of pharmaceutics.

[0096] When the microcapsules preparations according to the present invention are to be processed into an injectable preparation, they are dispersed in an aqueous vehicle together with a dispersing agent [e.g., Tween 80 (Astra Powder Co., U.S.A.), HCO 60 (Nikko Chemicals, Japan), carboxymethylcellulose, sodium alginate, etc.], preservative (e.g., methylparaben, propylparaben, benzyl alcohol, chlorobutanol, etc.), isotonizing agent (e.g., sodium chloride, glycerin, sorbitol, glucose, etc.), or the like. The vehicle may also be a vegetable oil (e.g., olive oil, sesame oil, peanut oil, cottonseed oil, corn oil, etc.), propylene glycol or the like. In this manner, an injectable preparation can be produced.

[0097] When the microcapsule preparations according to the present invention are to be processed into an oral preparation, they are mixed with an excipient (e.g., lactose, sucrose, starch, etc.), disintegrating agent (e.g., starch, calcium carbonate, etc.), binder (e.g., starch, gum arabic, carboxymethylcellulose, polyvinylpyrrolidone, hydroxypropylcellulose, etc.) and/or lubricant (e.g., talc, magnesium stearate, polyethyleneglycol 6000, etc.), and the mixtures are compressed in molds, and then if necessary, the preparations may be coated by a per se known method for the purpose of masking of the taste or providing them with enteric or sustained release properties. Coating agents which can be used are, for example, hydroxypropylmethylcellulose, ethylcellulose, hydroxymethylcellulose, hydroxypropylcellulose, polyoxyethlene glycol, tween 80, Pluronic F86, cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, Eudragit (Roehm, Germany; methacrylic acid-acrylic acid copolymer) and pigments (e.g., titanium oxide, ferric oxide, etc.).

[0098] To manufacture a topical preparation from the microcapsule preparations according to the present invention, they are provided solid, semi-solid or liquid state in the conventional manner. To manufacture the solid topical preparation for instance, the microcapsule preparation either as they are or together with an excipient (e.g., glucose, mannitol, starch, microcrystalline cellulose, etc.) and/or thickner (e.g., natural mucilages, cellulose derivatives, polyacrylates, etc.) are processed into powdery composition. To make a liquid composition, the microcapsule preparations are processed into an oily or aqueous suspension in substantially the same manner as in the case of injections. The semi-solid preparation may be an aqueous or oily gel or ointment. In any case, there may be added a pH adjusting agent (e.g., carbonic acid, phosphoric acid, citric acid, hydrochloric acid, sodium hydroxide, etc.), a preservative (e.g., p-hydroxybenzoic acid esters, chlorobutanol, benzalkonium chloride, etc.), or the like.

[0099] A suppository of the microcapsule preparation according to this invention, whether in oily or aqueous solid or semi-solid state or in liquid state, can be produced in the per se conventional manner. The kind of oleagenous base for such composition is optional only if it will not dissolve the microcapsule preparation. Thus, for example, higher fatty acid glycerides [e.g., cacao butter, Witepsol (Dynamit-Nobel, Germany), etc.], intermediate fatty acids [e.g., Miglyol

(Dynamit-Novel), etc.] and vegetable oils (e.g., sesame oil, soybean oil, cottonseed oil, etc.) may be mentioned. The aqueous base is exemplified by polyethylene glycol and propylene glycol, while the aqueous gel base may be selected from among natural mucilages, cellulose derivatives, vinyl polymers, polyacrylates, etc.

[0100] The dosage of the preparation according to this invention depends on the kind and amount of the active ingredient, dosage form, duration of drug release, recipient animal (e.g., warm blood animals such as mouse, rat, horse, cattle, man), and object of treatment. It is, however, sufficient to ensure that the effective dose of the active ingredient will be administered. The amount per dose to an adult (50 kg weight) may be selected from the range of about 1 mg to 10 g, preferably about 10 mg to 2 g, in terms of the weight of microcapsule preparation. For example, in case of microcapsule preparation containing TRH, TRH derivative or a salt thereof, the amount per dose to an adult (50 kg weight) may be selected from the range of about 5 mg to 5 g, preferably about 30 mg to 2 g, more preferably about 50 mg to 1 g, in term of the weight of microcapsule preparation.

[0101] When an injectable dosage form is employed, the volume of the suspension may be selected from the range of about 0.1 ml to 5 ml, preferably about 0.5 ml to 3 ml.

[0102] The polymer as a matrix for the microcapsule preparation in the present invention can be produced by a per se known method such as a method described in U.S. Patent Nos. 3,773,919, 4,273,920, 4,675,189, 4,767,628, 4,677,191, 4849,228 or EP-A-481732.

[0103] The microcapsule preparation of the present invention have, for example, the following characteristics.

(1) The prolonged release of drug in various dosage forms can be ensured. In particular, when a long term treatment with injections is required for the desired effect, the preparation helps achieve the desired pharmaceutical activities stably with an administration schedule of once a week or a month or even a year, instead of giving injections every day. Thus, compared with the conventional sustained release drugs, the prolonged release preparation of the present invention ensure longer sustained effects.

(2) When the injectable preparation are prepared by using the microcapsule preparation of the present invention, any surgical operation such as implantation is not required. The preparation can be administered subcutaneously or intramuscularly in quite the same manner as in the conventional injectable suspensions, and it is not required to remove them from the body.

Further, the injectable preparation can be administered directly to the tumor itself, the site of inflammation or the receptor region, so that systemic side effect can be controlled and the drug is allowed to efficiently act on the target organ over a longer period of time, thus making for increased drug efficacy. Furthermore, the injectable preparation can be used in intra-arterial administration in the vascular embolic therapy proposed by Kato et al., of cancer of the kidney and of the lung [Lancet, II, pp.479-480 (1979)].

(3) The release of the active component is continuous and, in the case of hormone antagonists, receptor antagonists or the like, stronger pharmacological activities are obtained than by daily administration.

(4) A drug can be entrapped into the microcapsule preparation more efficiently than those obtained by the conventional in-water drying or the W/O/W type three-phase emulsion. Further, finely pulverized even globular microcapsule preparation is obtained.

(5) The microcapsule preparation having a drug content of 10 to 50% which are hardly obtained by the conventional in-water drying process can be obtained.

(6) Since, compared with the conventional in-water drying process, a solvent removal rate is higher, the hardening rate of the microcapsule preparation having a stronger structure can be obtained. Therefore, the excess initial drug release rate after administration can be reduced.

(7) Aggregation and adhesion of the microcapsule preparation is remarkably diminished compared with spraying a solution containing only the drug and the polymer.

(8) It is possible to produce microcapsule preparations where aggregation of the microcapsules with each other and adhesion of the microcapsules preparations to a spray dryer or to a pipe part thereof is prevented by spraying the suspension or solution of a water-soluble inorganic salt, a water-soluble organic acid or a water-soluble salt of an organic acid as agent for preventing aggregation of the microcapsule preparation at a time while spraying the solution containing the drug and the polymer.

(9) Further, it is possible to produce microcapsule preparations having good dispersibility to a dispersing agent by further spraying a solution containing a non-ionic surfactant at a time while spraying the solution containing the drug and the polymer.

[0104] The following experiments and examples further illustrate the present invention. All percentages representing the concentration are weight/volume percents (W/V %) unless otherwise stated.

Experiment 1

[0105] Leuprorelin acetate (5g) was dissolved in water (50ml) at 60°C. To this solution was added a solution of lactic acidglycolic acid copolymer [lactic acid/glycolic acid : 75/25 (mole/mole), weight-average molecular weight in terms of polystyrene: 13000] (45g) dissolved in methylene chloride (75ml) . The mixture was emulsified with a small-size homogenizer (Polytron, manufactured by Kinematica, Switzerland) to obtain a W/O type emulsion.

(1) In-water drying process (the conventional method, hereinafter referred to as "A" process)

[0106] The above W/O type emulsion was converted into a (W/O)/W type emulsion in 0.5% polyvinyl alcohol (PVA) aqueous solution (2000ml) by using homogenizer. Then the emulsion was stirred slowly for 3 hours with a conventional propeller agitator. As methylene chloride was removed, (W/O) type microcapsules were collected by centrifugation. At the same time, the microcapsules were washed with purified water. The collected microcapsules were subjected to freeze-drying a whole day (24 hours) to obtain powder.

(2) Spray drying process (this invention, herein after referred to as "B" method)

[0107] The above W/O type emulsion was sprayed from one nozzle of a two-fluid nozzle at a flow rate 10 ml/min. and at the same time, 2% aqueous sodium chloride solution was sprayed from the other nozzle at a flow rate 10 ml/min. into a drying chamber of a spray dryer to obtain microcapsules as powder. The temperature at the entrance of the drying chamber was 95°C, the temperature at the outlet was 40°C and the air flow was 80 Kg/hr.

[0108] Various properties of the microcapsules produced by A and B processes were compared. The results are shown in Table 1.

Table 1

Comparison of Propertied of Microcapsules

Process	Surface state	Drug take-up[1)] (%)	Released amount for 1 day[2)] (%)	Distribution of particle size[3)] (µm)
A	many pores	5.3	78	5 to 200
B	few	99	24	5 to 40

1) Drug take-up was determined as follows.

The leuprorelin acetate in the microcapsules was determined by a high performance liquid chromatography (HPLC) procedure using Hitachi L-6300 equipment (Hitachi, Japan). Microcapsules (50mg) were dissolved in a mixture of dichloromethane (10ml) and 1/30M phosphate buffer (pH: 6.0, 20ml), and leuprorelin acetate extracted into the buffer was assayed by an HPLC procedure with an ultra violet (UV) detector under the following conditions;

column: Lichrosolb RP•18, 250mm in length with 4mm i.d.

column temperature: 30℃

mobile phase: a mixture of 0.25M acetonitrile (100ml) and methyl alcohol (150ml)

flow rate: 0.7 ml/minute

wave length: 280 nm.

Drug take-up (%) was calculated from the following formula;

$$\text{Drug Take-up (\%)} = \frac{\text{The leuprorelin acetate in the microcapsules}}{\text{Initial amount of leuprorelin acetate added into microcapsules}} \times 100$$

2) Released amount for 1 day (%) was determined as follows.

The microcapsules (50mg) were suspended in the release medium (10ml) consisting of 1/30M phosphate buffer (pH 7), containing 0.05% Tween-80 (Kao-Atlas, Tokyo) in a shaking bottle. This was shaken at 37℃ for one day by using a shaker (Taiyo Scientific Industrial Co., Tokyo).

The residual leuprorelin acetate in the microcapsules was determined after filtering the microcapsules through a 0.8 μm Millipore filter by the analytical method mentioned 1).

Released amount for 1 day (%) was determined by the following formula.

$$\text{Released amount for 1 day (\%)} = \left(1 - \frac{\text{The residual leuprorelin acetate in the microcapsules}}{\text{The initial amount of leuprorelin acetate in the microcapsules}}\right) \times 100$$

3) The distribution of particle size (μm) was determined as follows.

Microcapsules (10mg) were suspended in Isoton II solution

(Nikkaki Ltd., Japan). This suspension was subjected Multilizer (Coulter Inc. Co., U.S.A.) which was equipped with aperture tube of 100 µm or 280 µm to determine the distribution of particle size of the microcapsules.

[0109] As shown in Table 1, when the surface of the microcapsules was observed with a scanning electron microscope, many pores were observed on the surface of the microcapsules produced by "A" process, whereas pores were hardly observed on the surface of the microcapsules produced by "B" process and sodium chloride was evenly dispersed on the surface of the microcapsules. The take-up of the drug, i.e., leuprorelin acetate, was larger in "B" process than in "A" process. The amount of initially released drug for 1 day (an initial burst) in a release test of the microcapsules obtained by "B" process was larger than that obtained by "A" process.

[0110] The particle size distribution of the microcapsules obtained by "B" process was sharper than that obtained by "A" process. The time required for the production was about 24 hours in "A" process, while it was extremely short and about 10 minutes in "B" process. Thus, in view of the overall comparison, "B" process is an extremely useful production process of microcapsules compared with "A" process.

Experiment 2

[0111] Thyrotropin-releasing hormone (TRH) (0.5g) and lactic acidglycolic acid copolymer [lactic acid/glycolic acid: 75/25 (mole/mole), weight-average molecular weight: 14000] (9.5g) were dissolved homogeneously in a mixture of acetone (30ml) and water (2ml). The solution was sprayed from one nozzle of two-fluid nozzles set in the center of the spray dryer at a flow rate 10ml/min and, at the same time 4% aqueous solution of sorbitol, as an agent for preventing aggregation of the microcapsules, was sprayed from the other nozzle to give microcapsules as powder (hereinafter referred to as C process). Further, in the C process, instead of 4% aqueous solution of sorbitol, 3% aqueous solution of sodium chloride was sprayed as an agent for preventing aggregation of the microcapsule to give microcapsules powder (hereinafter referred to as D process). Furthermore, in the C process, instead of 4% aqueous solution of sorbitol, 3% aqueous solution of sodium chloride containing 0.0005% polysorbate 80 was sprayed to give microcapsules as powder (hereinafter referred to as E process).

[0112] Various properties of the microcapsules produced by C, D and E process were compared. The results are shown in Table 2.

Table 2

Comparison of Propertied of Microcapsules				
Process	Drug take-up (%)	Released amount for 1 day (%)	Distribution of particle size (µm)	Remaining water (%)
C	99	6	5 to 90	0.9
D	100	5	5 to 40	0.3
E	100	6	5 to 40	0.3

[0113] In any one of C, D and E processes, the take-up of the TRH was almost equally high (99 to 100%). In any one of microcapsules obtained by C, D and E process, the amount of released drug for 1 day in a release test in 1/30M phosphate buffer (pH 7.0) at 37°C was equally small (5 to 6%). The particle size distribution of the microcapsules obtained by D and E method were equal [5 to 40µm (mean 23µm) and 5 to 40µm (mean 24µm] and were sharper than that obtained by C method [5 to 90µm (mean 45µm)]. The remaining water of microcapsules obtained by any one of C, D and E was lower, 0.9%, 0.3% and 0.3%, than that of microcapsules obtained by in-water drying method, 1.0%.

[0114] When the surface of the microcapsules obtained by any one of C, D and E process was observed with a scanning electron microscope, pores were hardly observed. The microcapsules obtained by C process slightly adhered to each other owing to sorbitol on their surfaces. This caused the particle size distribution of the microcapsules obtained by C process to be large.

[0115] When the dispersibility of the microcapsules to a dispersing agent containing polysorbate 80 and mannitol, the following results were obtained. The dispersibility of the microcapsules obtained by C process was not good and

non-dispersed particles were observed after shaking. After storing for 24 hours, the microcapsules obtained by C process could not be dispersed. The dispersibility of the microcapsules obtained by D process was almost good, but a few non-dispersed particles were still observed and these could be dispersed by ultrasonication. The particles which sedimented after standing for 24 hours could be easily re-dispersed by shaking. The dispersibility of the microcapsules obtained by E process was good. The microcapsules could be easily dispersed, and the particles which sedimented after standing for 24 hours could be easily re-dispersed.

Example 1

[0116] Thyrotropin-releasing hormone (TRH) (0.4g) and lactic acidglycolic add copolymer [lactic acid/glycolic acid: 75/25 (mole/mole), weight-average molecular weight: 14000] (4.6g) were dissolved homogeneously in a mixture of methylene chloride (9.5ml), acetonitrile (10ml) and ethanol (0.5ml) or a mixture methylene chloride (12ml), acetonitrile (7.5ml) and ethanol (0.5ml). The solution was sprayed from one nozzle of two-fluid nozzles set in the center of the spray dryer at a flow rate of 10 ml/min and, at the same time, 1/5M phosphate buffer (containing disodium phosphate and sodium biphosphate, pH 7.4) was sprayed from the other nozzle for the prevention of aggregation of the microcapsules to give microcapsules as powder. The take-up of the TRH was 100% in each method. The amount of released TRH for 1 day in a release test of the microcapsules obtained by the above method was 15%. The dispersibility of the microcapsules was good. The average particle size of the microcapsules was 22μm.

Example 2

[0117] Thyrotropin-releasing hormone (TRH) (0.89) and lactic acid-glycolic add copolymer [lactic acid/glycolic add: 75/25 (mole/mole), weight-average molecular weight: 14000] (9.2g) were dissolved homogeneously in a mixture of acetonitrile (34.6ml) and water (5.3ml). The solution was sprayed from one nozzle of two-fluid nozzles set in the center of the spray dryer at a flow rate of 10 ml/min and, at the same time, 1/5M phosphate buffer (containing disodium phosphate and sodium biphosphate, pH 7.4) was sprayed from the other nozzle for the prevention of aggregation of the microcapsules to give microcapsules as powder. The take-up of the TRH was 100% in each method. The amount of released TRH for 1 day in a release test of the microcapsules obtained by the above method was 10%. The dispersibility of the microcapsules was good. The average particle size of the microcapsules was 23μm.

Example 3

[0118] Thyrotropin-releasing hormone (TRH) (1.6g) and lactic acid-glycolic acid copolymer [lactic acid/glycolic add: 75/25 (mole/mole) , weight-average molecular weight: 14000] (18.4g) were dissolved homogeneously in a mixture of acetonitrile (50ml) and water (10ml). The solution was sprayed from one nozzle of two-fluid nozzles set in the center of the spray dryer at a flow rate of 10 ml/min and, at the same time, 1/30M phosphate buffer (containing disodium phosphate and sodium biphosphate, pH 7.4) was sprayed from the other nozzle for the prevention of aggregation of the microcapsules to give microcapsules as powder. The take-up of the TRH was 100% in each method. The amount of released TRH for 1 day in a release test of the microcapsules obtained by the above method was 10%. The dispersibility of the microcapsules was good. The average particle size of the microcapsules was 22μm.

Example 4

[0119] Thyrotropin-releasing hormone (TRH) (0.8g) and lactic acid-glycolic acid copolymer [lactic acid/glycolic add: 75/25 (mole/mole), weight-average molecular weight: 14000] (9.2g) were dissolved homogeneously in a mixture of methylene chloride (24ml), ethanol (14ml) and water (2ml). The solution was sprayed from one nozzle of two-fluid nozzles set in the center of the spray dryer at a flow rate of 10 ml/min and, at the same time, a mixture of 1/10M phosphate buffer (containing disodium phosphate and sodium biphosphate, pH 7.4) and 1/5M aqueous sodium chloride solution was sprayed from the other nozzle for the prevention of aggregation of the microcapsules to produce microcapsules as a powder. The take-up of the TRH was 100% in each method. The amount of released TRH for 1 day in a release test of the microcapsules obtained by the above method was 18%. The dispersibility of the microcapsules was good. The average particle size of the microcapsules was 23μm.

Example 5

[0120] Thyrotropin-releasing hormone (TRH) (0.8g) and lactic acid-glycolic acid copolymer [lactic acid/glycolic acid: 75/25 (mole/mole), weight-average molecular weight: 14000] (9.2g) were dissolved homogeneously in a mixture of methylene chloride (10.6 ml) acetonitrile (25.5ml) and water (3.9ml). The solution was sprayed from one nozzle of two-

fluid nozzles set in the center of the spray dryer at a flow rate of 10 ml/min and, at the same time, 1/5M phosphate buffer (containing disodium phosphate and sodium biphosphate, pH 7.4) was sprayed from the other nozzle for the prevention of aggregation of the microcapsules to give microcapsules as a powder. The take-up of the TRH was 100% in each method. The amount of released TRH for 1 day in a release test of the microcapsules obtained by the above method was 18%. The dispersibility of the microcapsules was good. The average particle size of the microcapsules was 23μm.

Example 6

[0121] Cefotiam dihydrochloride (1g) was dissolved in water (3ml). To a solution of polylactic acid (weight-average molecular weight: 21000) (9g) in methylene chloride (20ml) was added the above solution, and the mixture was emulsified with a small-sized homogenizer (Polytron, Kinematica, Switerland) for 20 seconds. The resulting emulsion was sprayed from inner nozzle of the rotary disc having two-fluid nozzles, at the same time 3% aqueous sodium biphosphate solution containing 0.0001% polyoxyethylene hardened castor oil 60 was sprayed from the outer nozzle to give the microcapsules as a powder.

Example 7

[0122] Bleomycin hydrochloride (1g) and lactic acid-glycolic acid copolymer [lactic acid/glycolic acid: 50/50 (mole/mole), weight-average molecular weight: 10000] (9g) were dissolved in a mixture of water (5ml), acetonitrile (30ml) and ethanol (5ml). The solution was sprayed from inner nozzle of three-fluid nozzles for two-liquid spraying, at the same time, 2% aqueous sodium bicarbonate solution was sprayed from a middle nozzle and air was allowed to flow from an outer nozzle to give microcapsules.

[0123] According to the present invention, the microcapsule preparation having a high drug content, which are hardly obtained by the conventional in-water drying process can be continuously produced in a short time and on a large scale. According to the present invention, because the non-adhesive substance is dispersed on the surface of the microcapsule preparations, aggregation and adhesion of the microcapsule preparation is remarkably diminished compared with the conventional spray-drying method. Furthermore, it is possible to extremely improve a dispersibility of microcapsule preparations by dispersing or coating the surface of the microcapsule preparations with a non-ionic surfactant.

Claims

1. A microcapsule preparation comprising microcapsules of a biodegradable poly fatty acid ester which contain a drug and are wholly coated with a water-soluble inorganic salt, a water-soluble organic acid or a water-soluble salt of an organic acid with the proviso that said water-soluble organic acid is not carboxymethylcellulose or an amino acid and said water-soluble salt of an organic acid is not a salt of carboxymethylcellulose.

2. The preparation according to claim 1, wherein the poly fatty acid ester has a weight-average molecular weight of about 3,000 to 30,000.

3. The preparation according to claim 1, wherein the poly fatty acid ester has a dispersity of about 1.2 to 4.0.

4. The preparation according to claim 1, wherein the poly fatty acid ester is a member selected from the group consisting of homopolymers of α-hydroxycarboxylic acid, copolymers of two or more α-hydroxycarboxylic acid and a mixture thereof.

5. The preparation according to claim 4, wherein the homopolymer of α-hydroxycarboxylic acid is polylactic acid.

6. The preparation according to claim 4, wherein the copolymer of two or more α-hydroxycarboxylic acid is selected from the group consisting of copolymer of lactic acid/glycolic acid and copolymer of 2-hydroxybutyric acid/glycolic acid.

7. The preparation according to claim 4, wherein the mixture is a mixture of polylactic acid and copolymer of 2-hydroxybutyric acid/glycolic acid.

8. The preparation according to claim 1, wherein the drug is a member selected from the group consisting of peptides

having biological activities, antibiotics, antitumor agents, antipyretics, analgesics, anti-inflammatory agents, antitussive expectorants, sedatives, muscle relaxants, antiepileptic agents, antiulcer agents, antidepressants, antiallergic agents, cardiotonics, antiarrhythmic agents, vasodilators, hypotensive diuretics, antidiabetic agents, anticoagulants, hemostatics, antituberculous agents, hormone preparations, narcotic antagonists, bone resorption inhibitors and angiogenesis inhibiting substance.

9. The preparation according to claim 1, wherein the drug is a water-soluble drug having an n-octanol/water partition coefficient of not more than 1.

10. The preparation according to claim 1, wherein the drug is a member selected from the group consisting of thyrotropin-releasing hormone, their salts and derivatives.

11. The preparation according to claim 1, wherein the water-soluble inorganic salt, the water-soluble organic acid and the water-soluble salt of the organic acid are water-soluble materials which are applicable to humans and are solid at about 15 to 25°C and are non-adhesive in their dried state.

12. The preparation according to claim 1, wherein the water-soluble inorganic salt is a member selected from the group consisting of halogenated alkali metals, halogenated alkali-earth metals, halogenated ammoniums, alkali metal carbonates, alkali metal hydrogen carbonates, alkali-earth metal carbonates, ammonium carbonate, ammonium hydrogencarbonate, alkali metal phosphates, diammonium hydrogen phosphate, ammonium dihydrogen phosphate, alkali-earth metal oxide and alkali-earth metal hydroxide.

13. The preparation according to claim 1, wherein the water-soluble organic acid is selected from the group consisting of citric acid, tartaric acid, malic acid, succinic acid, benzoic acid, chondroitin sulfuric acid, dextran sulfuric acid, alginic acid and peptic acid.

14. The preparation according to claim 1, wherein the water-soluble salt of the organic acid is a member selected from the group consisting of alkali metal salts of organic acids and alkali-earth metal salts of organic acids excluding salts of carboxymethylcellulose.

15. The preparation according to claim 1, wherein the amount of water-soluble inorganic salt, the water-soluble organic acid or the water-soluble salt of the organic acid is about 0.001 to 100 times the weight of the poly fatty acid ester.

16. The preparation according to claim 1, wherein the particle size of the microcapsule preparation is about 0.5 to 400 μm.

17. A method for producing a microcapsule preparation which comprises spraying a solution of a biodegradable poly fatty acid ester containing a drug and a solution of a water-soluble inorganic salt, a water-soluble organic acid or a water-soluble salt of an organic acid separately from different nozzles, with the proviso that when the solution of polymer containing a drug is a W/O type emulsion the water-soluble organic acid is not carboxymethylcellulose or an amino acid or the water-soluble salt of an organic acid is not a salt of carboxymethylcellulose, and contacting them with each other in a spray dryer to produce microcapsules of the poly fatty acid ester which contains the drug and are coated wholly with the water-soluble inorganic salt, the water-soluble organic acid or the water-soluble salt of the organic acid.

18. The method according to claim 17, wherein the solution of the poly fatty acid ester containing the drug is a homogenous solution.

19. The method according to claim 17, wherein the solution of the poly fatty acid ester containing the drug is a dispersion solution in which a part or whole of the drug or the poly fatty acid ester is in a state of dispersion.

20. The method according to claim 17, wherein the solution of the poly fatty acid ester containing the drug is an O/W, W/O, W/O/W or O/W/O type emulsion comprising a solution containing the drug and/or the poly fatty acid ester.

21. The method according to claim 17, wherein the solution of the poly fatty acid ester containing the drug is an O/W, W/O, W/O/W or O/W/O type emulsion comprising a dispersion solution in which part of whole of the drug or the poly fatty acid ester is in a state of dispersion.

22. The method according to claim 17, wherein the poly fatty acid ester has a weight-average molecular weight of about 3,000 to 30,000.

23. The method according to claim 17, wherein the poly fatty acid ester has a dispersity of about 1.2 to 4.0.

24. The method according to claim 17, wherein the poly fatty acid ester is a member selected from the group consisting of homopolymers of α-hydroxycarboxylic acid, copolymers of two or more α-hydroxycarboxylic acid and a mixture thereof.

25. The method according to claim 24, wherein the homopolymer of α-hydroxycarboxylic acid is polylactic acid.

26. The method according to claim 24, wherein the copolymer of two or more α-hydroxycarboxylic acid is selected from the group consisting of copolymer of lactic acid/glycolic acid and copolymer of 2-hydroxybutyric acid/glycolic acid.

27. The method according to claim 24, wherein the mixture is a mixture of polylactic acid and copolymer of 2-hydroxybutyric acid/glycolic acid.

28. The method according to claim 17, wherein the drug is a member selected from the group consisting of peptides having biological activities, antibiotics, antitumor agents, antipyretics, analgesics, anti-inflammatory agents, antitussive expectorants, sedatives, muscle relaxants, antiepileptic agents, antiulcer agents, antidepressants, antiallergic agents, cardiotonics, antiarrhythmic agents, vasodilators, hypotensive diuretics, antidiabetic agents, anticoagulants, hemostatics, antituberculous agents, hormone preparations, narcotic antagonists, bone resorption inhibitors and angiogenesis inhibiting substance.

29. The method according to claim 17, wherein the drug is a water-soluble drug having an n-octanol/water partition coefficient of not more than 1.

30. The method according to claim 17, wherein the drug is a member selected from the group consisting of thyrotropin-releasing hormone, their salts and derivatives.

31. The method according to claim 17, wherein the water-soluble inorganic salt, the water-soluble organic acid and the water-soluble salt of the organic acid are water-soluble materials which are applicable to humans and are solid at about 15 to 25°C and are non-adhesive in their dried state.

32. The method according to claim 17, wherein the water-soluble inorganic salt is a member selected from the group consisting halogenated alkali metals, halogenated alkali-earth metals, halogenated ammoniums, alkali metal carbonates, alkali metal hydrogen carbonates, alkali-earth metal carbonates, ammoniumcarbonate, ammonium hydrogencarbonate, alkali metal phosphates, diammonium hydrogen phosphate, ammonium dihydrogen phosphate, alkali-earth metal oxide and alkali-earth metal hydroxide.

33. The method according to claim 17, wherein the water-soluble organic acid is selected from the group consisting of citric acid, tartaric acid, malic acid, succinic acid, benzoic acid, chondroitin sulfuric acid, dextran sulfuric acid, alginic acid and peptic acid.

34. The method according to claim 17, wherein the water-soluble salt of the organic acid is a member selected from the group consisting of alkali metal salts of organic acids and alkali-earth metal salts of organic acids, excluding salts of carboxymethylcellulose.

35. The method according to claim 17, wherein the amount of the water-soluble inorganic salt, the water-soluble organic acid or the water-soluble salt of the organic acid is about 0.001 to 100 times the weight of the poly fatty acid ester.

36. The method according to claim 17, wherein the particle size of the microcapsule preparation is about 0.5 to 400 μm.

37. The method according to claim 17, wherein the solution of the water-soluble inorganic salt, the water-soluble organic acid or the water-soluble salt of the organic acid is an aqueous solution.

38. The method according to claim 17, wherein the solution of the water-soluble inorganic salt, the water-soluble

organic acid or the water-soluble salt of the organic acid contains a surfactant.

39. The method according to claim 17, wherein the surfactant is a non-ionic surfactant.

40. The method according to claim 17, wherein a solution of surfactant is sprayed separately from a different nozzle and contacting it with the solution of poly fatty acid ester containing the drug and the solution of the water-soluble inorganic salt, the water-soluble organic acid or the water-soluble salt of the organic acid in the spray dryer.

41. The method according to claim 40, wherein the surfactant is a non-ionic surfactant.

42. The use of a water-soluble inorganic salt, a water-soluble organic acid or a water-soluble salt of an organic acid for preventing aggregation of a microcapsule in a process for production of a microcapsule preparation comprising spraying a solution of a biodegradable poly fatty acid ester containing a drug in a spray dryer, which comprises spraying a solution of the water-soluble inorganic salt, the water-soluble organic acid or the water-soluble salt of the organic acid separately from different nozzles and contacting it with the solution of the poly fatty acid ester containing the drug, wherein the water-soluble organic acid is not carboxymethylcellulose or an amino acid and the water-soluble salt of an organic acid is not a salt of carboxymethylcellulose.

Patentansprüche

1. Mikrokapselpräparat, umfassend Mikrokapseln aus einem biologisch abbaubaren Polyfettsäureester, die einen Wirkstoff enthalten und die ganz mit einem wasserlöslichen anorganischen Salz, einer wasserlöslichen organischen Säure oder einem wasserlöslichen Salz einer organischen Säure überzogen sind, mit der Maßgabe, dass es sich bei der wasserlöslichen organischen Säure nicht um Carboxymethylcellulose oder eine Aminosäure handelt und das wasserlösliche Salz einer organischen Säure kein Salz von Carboxymethylcellulose ist.

2. Präparat gemäß Anspruch 1, wobei der Polyfettsäureester ein Gewichtsmittel des Molekulargewichts von etwa 3000 bis 30 000 hat.

3. Präparat gemäß Anspruch 1, wobei der Polyfettsäureester eine Dispersität von etwa 1,2 bis 4,0 hat.

4. Präparat gemäß Anspruch 1, wobei der Polyfettsäureester aus der Gruppe ausgewählt ist, die aus Homopolymeren einer α-Hydroxycarbonsäure, Copolymeren von zwei oder mehr α-Hydroxycarbonsäuren und einem Gemisch davon besteht.

5. Präparat gemäß Anspruch 4, wobei es sich bei dem Homopolymer einer α-Hydroxycarbonsäure um Polymilchsäure handelt.

6. Präparat gemäß Anspruch 4, wobei das Copolymer von zwei oder mehr α-Hydroxycarbonsäuren aus der Gruppe ausgewählt ist, die aus einem Copolymer von Milchsäure/Glycolsäure und einem Copolymer von 2-Hydroxybuttersäure/Glycolsäure besteht.

7. Präparat gemäß Anspruch 4, wobei das Gemisch ein Gemisch aus Polymilchsäure und einem Copolymer von 2-Hydroxybuttersäure/Glycolsäure ist.

8. Präparat gemäß Anspruch 1, wobei der Wirkstoff aus der Gruppe ausgewählt ist, die aus biologisch aktiven Peptiden, Antibiotika, Antitumormitteln, Antipyretika, Analgetika, entzündungshemmenden Mitteln, antitussiven Expektorantien, Sedativa, Muskelrelaxantien, Antiepileptika, Antiulcusmitteln, Antidepressiva, Antiallergika, Cardiotonika, Antiarrhythmika, Vasodilatoren, hypotensiven Diuretika, Antidiabetika, Antikoagulantien, Hämostatika, Antituberkulosemitteln, Hormonpräparaten, Antagonisten von Narkotika, Knochenresorptionsinhibitoren und einer Angiogenese-hemmenden Substanz besteht.

9. Präparat gemäß Anspruch 1, wobei der Wirkstoff ein wasserlöslicher Wirkstoff mit einem n-Octanol/Wasser-Verteiiungskoeffizienten von nicht mehr als 1 ist.

10. Präparat gemäß Anspruch 1, wobei der Wirkstoff aus der Gruppe ausgewählt ist, die aus Thyrotropin-freisetzendem Hormon, dessen Salzen und Derivaten besteht.

11. Präparat gemäß Anspruch 1, wobei das wasserlösliche anorganische Salz, die wasserlösliche organische Säure und das wasserlösliche Salz der organischen Säure wasserlösliche Stoffe sind, die man dem Menschen verabreichen kann, und bei etwa 15 bis 25°C fest und in getrocknetem Zustand nicht klebrig sind.

12. Präparat gemäß Anspruch 1, wobei das wasserlösliche anorganische Salz aus der Gruppe ausgewählt ist, die aus halogenierten Alkalimetallen, halogenierten Erdalkalimetallen, halogenierten Ammoniumspezies, Alkalimetallcarbonaten, Alkalimetallhydrogencarbonaten, Erdalkalimetallcarbonaten, Ammoniumcarbonat, Ammoniumhydrogencarbonat, Alkalimetallphosphaten, Diammoniumhydrogenphosphat, Ammoniumdihydrogenphosphat, Erdalkalimetalloxid und Erdalkalimetallhydroxid besteht.

13. Präparat gemäß Anspruch 1, wobei die wasserlösliche organische Säure aus der Gruppe ausgewählt ist, die aus Zitronensäure, Weinsäure, Äpfelsäure, Bernsteinsäure, Benzoesäure, Chondroitinschwefelsäure, Dextranschwefelsäure, Alginsäure und Peptinsäure besteht.

14. Präparat gemäß Anspruch 1, wobei das wasserlösliche Salz der organischen Säure aus der Gruppe ausgewählt ist, die aus Alkalimetallsalzen organischer Säuren und Erdalkalimetallsalzen organischer Säuren besteht, wobei Salze von Carboxymethylcellulose ausgeschlossen sind.

15. Präparat gemäß Anspruch 1, wobei die Menge des wasserlöslichen anorganischen Salzes, der wasserlöslichen organischen Säure und des wasserlöslichen Salzes der organischen Säure dem etwa 0,001- bis 100fachen des Gewichts des Polyfettsäureesters entspricht.

16. Präparat gemäß Anspruch 1, wobei die Teilchengröße des Mikrokapselpräparats etwa 0,5 bis 400 μm beträgt.

17. Verfahren zur Herstellung eines Mikrokapselpräparats, umfassend das getrennte Sprühen einer Lösung eines biologisch abbaubaren Polyfettsäureesters, die einen Wirkstoff enthält, und einer Lösung eines wasserlöslichen anorganischen Salzes, einer wasserlöslichen organischen Säure oder eines wasserlöslichen Salzes einer organischen Säure aus verschiedenen Düsen, mit der Maßgabe, dass es sich, wenn die Polymerlösung, die einen Wirkstoff enthält, eine Emulsion des W/O-Typs ist, bei der wasserlöslichen organischen Säure nicht um Carboxymethylcellulose oder eine Aminosäure handelt oder das wasserlösliche Salz einer organischen Säure kein Salz von Carboxymethylcellulose ist, und das Miteinander-in-Kontakt-Bringen derselben in einem Sprühtrockner unter Bildung von Mikrokapseln aus dem Polyfettsäureester, die den Wirkstoff enthalten und die ganz mit dem wasserlöslichen anorganischen Salz, der wasserlöslichen organischen Säure oder dem wasserlöslichen Salz der organischen Säure überzogen sind.

18. Verfahren gemäß Anspruch 17, wobei die den Wirkstoff enthaltende Lösung des Polyfettsäureesters eine homogene Lösung ist.

19. Verfahren gemäß Anspruch 17, wobei die den Wirkstoff enthaltende Lösung des Polyfettsäureesters eine Dispersionslösung ist, in der sich ein Teil oder die Gesamtmenge des Wirkstoffs oder des Polyfettsäureesters in dispergiertem Zustand befinden.

20. Verfahren gemäß Anspruch 17, wobei die den Wirkstoff enthaltende Lösung des Polyfettsäureesters eine Emulsion des O/W-, W/O-, W/O/W- oder O/W/O-Typs ist, die eine Lösung umfasst, die den Wirkstoff und/oder den Polyfettsäureester enthält.

21. Verfahren gemäß Anspruch 17, wobei die den Wirkstoff enthaltende Lösung des Polyfettsäureesters eine Emulsion des O/W-, W/O-, W/O/W- oder O/W/O-Typs ist, die eine Dispersionslösung umfasst, in der sich ein Teil oder die Gesamtmenge des Wirkstoffs oder des Polyfettsäureesters in dispergiertem Zustand befinden.

22. Verfahren gemäß Anspruch 17, wobei der Polyfettsäureester ein Gewichtsmittel des Molekulargewichts von etwa 3000 bis 30 000 hat.

23. Verfahren gemäß Anspruch 17, wobei der Polyfettsäureester eine Dispersität von etwa 1,2 bis 4,0 hat.

24. Verfahren gemäß Anspruch 17, wobei der Polyfettsäureester aus der Gruppe ausgewählt ist, die aus Homopolymeren einer α-Hydroxycarbonsäure, Copolymeren von zwei oder mehr α-Hydroxycarbonsäuren und einem Gemisch davon besteht.

25. Verfahren gemäß Anspruch 24, wobei es sich bei dem Homopolymer einer α-Hydroxycarbonsäure um Polymilchsäure handelt.

26. Verfahren gemäß Anspruch 24, wobei das Copolymer von zwei oder mehr α-Hydroxycarbonsäuren aus der Gruppe ausgewählt ist, die aus einem Copolymer von Milchsäure/Glycolsäure und einem Copolymer von 2-Hydroxybuttersäure/Glycolsäure besteht.

27. Verfahren gemäß Anspruch 24, wobei das Gemisch ein Gemisch aus Polymilchsäure und einem Copolymer von 2-Hydroxybuttersäure/Glycolsäure ist.

28. Verfahren gemäß Anspruch 17, wobei der Wirkstoff aus der Gruppe ausgewählt ist, die aus biologisch aktiven Peptiden, Antibiotika, Antitumormitteln, Antipyretika, Analgetika, entzündungshemmenden Mitteln, antitussiven Expektorantien, Sedativa, Muskelrelaxantien, Antiepileptika, Antiulcusmitteln, Antidepressiva, Antiallergika, Cardiotonika, Antiarrhythmika, Vasodilatoren, hypotensiven Diuretika, Antidiabetika, Antikoagulantien, Hämostatika, Antituberkulosemitteln, Hormonpräparaten, Antagonisten von Narkotika, Knochenresorptionsinhibitoren und einer Angiogenese-hemmenden Substanz besteht.

29. Verfahren gemäß Anspruch 17, wobei der Wirkstoff ein wasserlöslicher Wirkstoff mit einem n-Octanol/Wasser-Verteilungskoeffizienten von nicht mehr als 1 ist.

30. Verfahren gemäß Anspruch 17, wobei der Wirkstoff aus der Gruppe ausgewählt ist, die aus Thyrotropin-freisetzendem Hormon, dessen Salzen und Derivaten besteht.

31. Verfahren gemäß Anspruch 17, wobei das wasserlösliche anorganische Salz, die wasserlösliche organische Säure und das wasserlösliche Salz der organischen Säure wasserlösliche Stoffe sind, die man dem Menschen verabreichen kann, und bei etwa 15 bis 25°C fest und in getrocknetem Zustand nicht klebrig sind.

32. Verfahren gemäß Anspruch 17, wobei das wasserlösliche anorganische Salz aus der Gruppe ausgewählt ist, die aus halogenierten Alkalimetallen, halogenierten Erdalkalimetallen, halogenierten Ammoniumspezies, Alkalimetallcarbonaten, Alkalimetallhydrogencarbonaten, Erdalkalimetallcarbonaten, Ammoniumcarbonat, Ammoniumhydrogencarbonat, Alkalimetallphosphaten, Diammoniumhydrogenphosphat, Ammoniumdihydrogenphosphat, Erdalkalimetalloxid und Erdalkalimetallhydroxid besteht.

33. Verfahren gemäß Anspruch 17, wobei die wasserlösliche organische Säure aus der Gruppe ausgewählt ist, die aus Zitronensäure, Weinsäure, Äpfelsäure, Bernsteinsäure, Benzoesäure, Chondroitinschwefelsäure, Dextranschwefelsäure, Alginsäure und Peptinsäure besteht.

34. Verfahren gemäß Anspruch 17, wobei das wasserlösliche Salz der organischen Säure aus der Gruppe ausgewählt ist, die aus Alkalimetallsalzen organischer Säuren und Erdalkalimetallsalzen organischer Säuren besteht, wobei Salze von Carboxymethylcellulose ausgeschlossen sind.

35. Verfahren gemäß Anspruch 17, wobei die Menge des wasserlöslichen anorganischen Salzes, der wasserlöslichen organischen Säure und des wasserlöslichen Salzes der organischen Säure dem etwa 0,001- bis 100fachen des Gewichts des Polyfettsäureesters entspricht.

36. Verfahren gemäß Anspruch 17, wobei die Teilchengröße des Mikrokapselpräparats etwa 0,5 bis 400 µm beträgt.

37. Verfahren gemäß Anspruch 17, wobei die Lösung des wasserlöslichen anorganischen Salzes, der wasserlöslichen organischen Säure oder des wasserlöslichen Salzes der organischen Säure eine wässrige Lösung ist.

38. Verfahren gemäß Anspruch 17, wobei die Lösung des wasserlöslichen anorganischen Salzes, der wasserlöslichen organischen Säure oder des wasserlöslichen Salzes der organischen Säure ein Tensid enthält.

39. Verfahren gemäß Anspruch 17, wobei das Tensid ein nichtionisches Tensid ist.

40. Verfahren gemäß Anspruch 17, wobei eine Tensidlösung getrennt aus einer anderen Düse gesprüht wird und in dem Sprühtrockner mit der Lösung des Polyfettsäureesters, die den Wirkstoff enthält, und der Lösung des wasserlöslichen anorganischen Salzes, der wasserlöslichen organischen Säure oder des wasserlöslichen Salzes der

organischen Säure in Kontakt gebracht wird.

41. Verfahren gemäß Anspruch 40, wobei das Tensid ein nichtionisches Tensid ist.

42. Verwendung eines wasserlöslichen anorganischen Salzes, einer wasserlöslichen organischen Säure oder eines wasserlöslichen Salzes einer organischen Säure zur Verhinderung der Aggregation einer Mikrokapsel in einem Verfahren zur Herstellung eines Mikrokapselpräparats, das das Sprühen einer Lösung eines biologisch abbaubaren Polyfettsäureesters, die einen Wirkstoff enthält, in einem Sprühtrockner umfasst, umfassend das getrennte Sprühen einer Lösung des wasserlöslichen anorganischen Salzes, der wasserlöslichen organischen Säure oder des wasserlöslichen Salzes einer organischen Säure aus verschiedenen Düsen und das In-Kontakt-Bringen derselben mit der Lösung des Polyfettsäureesters, die den Wirkstoff enthält, wobei es sich bei der wasserlöslichen organischen Säure nicht um Carboxymethylcellulose oder eine Aminosäure handelt und das wasserlösliche Salz einer organischen Säure kein Salz von Carboxymethylcellulose ist.

Revendications

1. Préparation de microcapsules comprenant des microcapsules d'un ester de polyacide gras biodégradable contenant un médicament, qui sont revêtues entièrement d'un sel minéral soluble dans l'eau, d'un acide organique soluble dans l'eau ou d'un sel soluble dans l'eau d'un acide organique, avec la condition que ledit acide organique soluble dans l'eau n'est pas la carboxylméthylcellulose ou un acide aminé et que ledit sel soluble dans l'eau d'un acide organique n'est pas un sel de la carboxylméthylcellulose.

2. Préparation selon la revendication 1, dans laquelle l'ester de polyacide gras a un poids moléculaire moyen pondéral d'environ 3 000 à 30 000.

3. Préparation selon la revendication 1, dans laquelle l'ester de polyacide gras a une dispersibilité d'environ 1,2 à 4,0.

4. Préparation selon la revendication 1, dans laquelle l'ester de polyacide gras est un représentant du groupe consistant en homopolymères d'acide α-hydroxycarboxylique, copolymères de deux ou plusieurs acides α-hydroxycarboxyliques et mélanges de ceux-ci.

5. Préparation selon la revendication 4, dans laquelle l'homopolymère d'acide α-hydroxycarboxylique est l'acide polylactique.

6. Préparation selon la revendication 4, dans laquelle le copolymère de deux ou plusieurs acides α-hydroxycarboxyliques est un représentant du groupe consistant en copolymères d'acide lactique/acide glycolique et copolymères d'acide 2-hydroxybutyrique/acide glycolique.

7. Préparation selon la revendication 4, dans laquelle le mélange est un mélange d'acide polylactique et de copolymère d'acide 2-hydroxybutyrique/acide glycolique.

8. Préparation selon la revendication 1, dans laquelle le médicament est un représentant du groupe consistant en peptides doués d'activité biologique, antibiotiques, agents antitumoraux, agents antipyrétiques, analgésiques, anti-inflammatoires, expectorants antitussifs, sédatifs, relaxateurs musculaires, agents antiépileptiques, agents antiulcéreux, antidépresseurs, agents antiallergiques, cardiotoniques, agents antiarythmiques, vasodilatateurs, diurétiques hypotenseurs, agents antidiabétiques, anticoagulants, hémostatiques, agents antituberculeux, préparations hormonales, antagonistes des narcotiques, inhibiteurs de la résorption osseuse et substances inhibant l'angiogenèse.

9. Préparation selon la revendication 1, dans laquelle le médicament est un médicament soluble dans l'eau dont le coefficient de répartition dans le n-octanol/eau n'est pas supérieur à 1.

10. Préparation selon la revendication 1, dans laquelle le médicament est un représentant du groupe consistant en l'hormone libérant la thyréostimuline, les sels et les dérivés de celle-ci.

11. Préparation selon la revendication 1, dans laquelle le sel minéral soluble dans l'eau, l'acide organique soluble dans l'eau et le sel soluble dans l'eau d'un acide organique sont des substances solubles dans l'eau qui sont

susceptibles d'utilisation chez l'homme et qui sont à l'état solide à environ 15 à 25°C et ne sont pas collantes à l'état sec.

12. Préparation selon la revendication 1, dans laquelle le sel minéral soluble dans l'eau est un représentant du groupe consistant en halogénures de métal alcalin, halogénures de métal alcalino-terreux, halogénures d'ammonium, carbonates de métal alcalin, hydrogénocarbonates de métal alcalin, carbonates de métal alcalino-terreux, carbonate d'ammonium, hydrogénocarbonate d'ammonium, phosphates de métal alcalin, hydrogénophosphate de diammonium, dihydrogénophosphate d'ammonium, oxyde de métal alcalino-terreux et hydroxyde de métal alcalino-terreux.

13. Préparation selon la revendication 1, dans laquelle l'acide organique soluble dans l'eau est un représentant du groupe consistant en acide citrique, acide tartrique, acide malique, acide succinique, acide benzoïque, acide chondroïtinesulfurique, acide dextranesulfurique, acide alginique et acide peptique.

14. Préparation selon la revendication 1, dans laquelle le sel soluble dans l'eau d'un acide organique est un représentant du groupe consistant en sels de métal alcalin d'acides organiques et sels de métal alcalino-terreux d'acides organiques, à l'exception des sels de la carboxyméthylcellulose.

15. Préparation selon la revendication 1, dans laquelle la quantité de sel minéral soluble dans l'eau, d'acide organique soluble dans l'eau ou de sel soluble dans l'eau d'un acide organique est d'environ 0,001 à 100 fois le poids de l'ester de polyacide gras.

16. Préparation selon la revendication 1, dans laquelle la dimension des particules de la préparation de microcapsules est d'environ 0,5 à 400 μm.

17. Procédé de fabrication d'une préparation de microcapsules, selon lequel on pulvérise séparément, au moyen de buses différentes, une solution d'un ester de polyacide gras biodégradable contenant un médicament et une solution d'un sel minéral soluble dans l'eau, d'un acide organique soluble dans l'eau ou d'un sel soluble dans l'eau d'un acide organique, avec la condition que lorsque la solution de polymère contenant un médicament est une émulsion de type eau/huile, l'acide organique soluble dans l'eau n'est pas la carboxylméthylcellulose ou un acide aminé ou le sel soluble dans l'eau d'un acide organique n'est pas un sel de la carboxyméthylcellulose, et l'on met en contact l'une et l'autre solution dans un dessiccateur-pulvérisateur, ce par quoi l'on obtient des microcapsules de l'ester de polyacide gras contenant le médicament, qui sont revêtues entièrement du sel minéral soluble dans l'eau, de l'acide organique soluble dans l'eau ou du sel soluble dans l'eau de l'acide organique.

18. Procédé selon la revendication 17, dans lequel la solution de l'ester de polyacide gras contenant le médicament est une solution homogène.

19. Procédé selon la revendication 17, dans lequel la solution de l'ester de polyacide gras contenant le médicament est une dispersion dans laquelle le médicament ou le polymère se trouve, partiellement ou entièrement, à l'état dispersé.

20. Procédé selon la revendication 17, dans lequel la solution de l'ester de polyacide gras contenant le médicament est une émulsion de type huile/eau, eau/huile, eau/huile/eau ou huile/eau/huile, qui comprend une solution contenant le médicament et/ou le l'ester de polyacide gras.

21. Procédé selon la revendication 17, dans lequel la solution de l'ester de polyacide gras contenant le médicament est une émulsion de type huile/eau, eau/huile, eau/huile/eau ou huile/eau/huile, qui comprend une solution dispersée dans laquelle le médicament ou l'ester de polyacide gras se trouve, partiellement ou entièrement, à l'état dispersé.

22. Procédé selon la revendication 17, dans lequel l'ester de polyacide gras a un poids moléculaire moyen pondéral d'environ 3 000 à 30 000.

23. Procédé selon la revendication 17, dans lequel l'ester de polyacide gras a une dispersibilité d'environ 1,2 à 4,0.

24. Procédé selon la revendication 17, dans lequel l'ester de polyacide gras est un représentant du groupe consistant en homopolymères d'acide α-hydroxycarboxylique, copolymères de deux ou plusieurs acides α-hydroxycarboxy-

liques et mélanges de ceux-ci.

25. Procédé selon la revendication 24, dans lequel l'homopolymère d'acide α-hydroxycarboxylique est l'acide polylactique.

26. Procédé selon la revendication 24, dans lequel le copolymère de deux ou plusieurs acides α-hydroxycarboxyliques est un représentant du groupe consistant en copolymères d'acide lactique/acide glycolique et copolymères d'acide 2-hydroxybutyrique/acide glycolique.

27. Procédé selon la revendication 24, dans lequel le mélange est un mélange d'acide polylactique et de copolymère d'acide 2-hydroxybutyrique/acide glycolique.

28. Procédé selon la revendication 17, dans lequel le médicament est un représentant du groupe consistant en peptides doués d'activité biologique, antibiotiques, agents antitumoraux, agents antipyrétiques, analgésiques, antiinflammatoires, expectorants antitussifs, sédatifs, relaxateurs musculaires, agents antiépileptiques, agents antiulcéreux, antidépresseurs, agents antiallergiques, cardiotoniques, agents antiarythmiques, vasodilatateurs, diurétiques hypotenseurs, agents antidiabétiques, anticoagulants, hémostatiques, agents antituberculeux, préparations hormonales, antagonistes des narcotiques, inhibiteurs de la résorption osseuse et substances inhibant l'angiogenèse.

29. Procédé selon la revendication 17, dans lequel le médicament est un médicament soluble dans l'eau dont le coefficient de répartition dans le n-octanol/eau n'est pas supérieur à 1.

30. Procédé selon la revendication 17, dans lequel le médicament est un représentant du groupe consistant en l'hormone libérant la thyréotropine, les sels et les dérivés de celle-ci.

31. Procédé selon la revendication 17, dans lequel le sel minéral soluble dans l'eau, l'acide organique soluble dans l'eau et le sel soluble dans l'eau d'un acide organique sont des substances solubles dans l'eau qui sont susceptibles d'utilisation chez l'homme et qui sont à l'état solide à environ 15 à 25°C et ne sont pas collantes à l'état sec.

32. Procédé selon la revendication 17, dans lequel le sel minéral soluble dans l'eau est un représentant du groupe consistant en halogénures de métal alcalin, halogénures de métal alcalino-terreux, halogénures d'ammonium, carbonates de métal alcalin, hydrogénocarbonates de métal alcalin, carbonates de métal alcalino-terreux, carbonate d'ammonium, hydrogénocarbonate d'ammonium, phosphates de métal alcalin, hydrogénophosphate de diammonium, dihydrogénophosphate d'ammonium, oxyde de métal alcalino-terreux et hydroxyde de métal alcalino-terreux.

33. Procédé selon la revendication 17, dans lequel l'acide organique soluble dans l'eau est un représentant du groupe consistant en acide citrique, acide tartrique, acide malique, acide succinique, acide benzoïque, acide chondroïtinesulfurique, acide dextranesulfurique, acide alginique et acide peptique.

34. Procédé selon la revendication 17, dans lequel le sel soluble dans l'eau d'un acide organique est un représentant du groupe consistant en sels de métal alcalin d'acides organiques et sels de métal alcalino-terreux d'acides organiques, à l'exception des sels de la carboxyméthylcellulose.

35. Procédé selon la revendication 17, dans lequel la quantité de sel minéral soluble dans l'eau, d'acide organique soluble dans l'eau ou de sel soluble dans l'eau d'un acide organique est d'environ 0,001 à 100 fois le poids de l'ester de polyacide gras.

36. Procédé selon la revendication 17, dans lequel la dimension des particules de la préparation de microcapsules est d'environ 0,5 à 400 μm.

37. Procédé selon la revendication 17, dans lequel la solution de sel minéral soluble dans l'eau, d'acide organique soluble dans l'eau ou de sel soluble dans l'eau d'un acide organique est une solution aqueuse.

38. Procédé selon la revendication 17, dans lequel la solution de sel minéral soluble dans l'eau, d'acide organique soluble dans l'eau ou de sel soluble dans l'eau d'un acide organique contient un agent tensioactif.

39. Procédé selon la revendication 17, dans lequel l'agent tensioactif est un agent tensioactif non ionique.

40. Procédé selon la revendication 17, dans lequel la solution d'agent tensioactif est pulvérisée séparément, au moyen d'une buse différente, et elle est mise en contact dans le dessiccateur-pulvérisateur avec la solution de l'ester de polyacide gras contenant le médicament et la solution de sel minéral soluble dans l'eau, d'acide organique soluble dans l'eau ou de sel soluble dans l'eau d'un acide organique.

41. Procédé selon la revendication 40, dans lequel l'agent tensioactif est un agent tensioactif non ionique.

42. Utilisation d'un sel minéral soluble dans l'eau, d'un acide organique soluble dans l'eau ou d'un sel soluble dans l'eau d'un acide organique afin de prévenir l'agglutination de microcapsules dans un procédé de fabrication d'une préparation de microcapsules, selon lequel on pulvérise dans un dessiccateur-pulvérisateur une solution d'un ester de polyacide gras biodégradable contenant un médicament, **caractérisée en ce que** l'on pulvérise séparément, au moyen de buses différentes, une solution du sel minéral soluble dans l'eau, de l'acide organique soluble dans l'eau ou du sel soluble dans l'eau d'un acide organique et on la met en contact avec la solution d'ester de polyacide gras contenant le médicament, avec la condition que l'acide organique soluble dans l'eau n'est pas la carboxyméthylcellulose ou un acide aminé et que le sel soluble dans l'eau d'un acide organique n'est pas un sel de la carboxyméthylcellulose.